PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2008/000614	05.05.2008	07.05.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C12M1/00 C12M1/04 C12M3/00

Applicant
PROTALIX LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	see form PCT/ISA/210	Böhm, Ingo Telephone No. +49 30 25901-333

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-62
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-62
Industrial applicability (IA)	Yes:	Claims	1-62
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

1 Reference is made to the following document:

D1 : US 2005/272146 A1 (HODGE GEOFFREY [US] ET AL) 8 December 2005 (2005-12-08)

2 INDEPENDENT CLAIMS 1,36,54

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-62 is not new in the sense of Article 33(2) PCT.

2.1

Document D1 discloses bioreactor systems and present an improved disposable bioreactor system.

In particular, embodiments of the invention of D1 provide mixing, aeration and/or process control, to which a substantial number (e.g., most) of the typical utilities required to run a bioreactor have been eliminated.

Moreover, some embodiments of D1 provide a total disposable solution-all contact surfaces, including probes and sensor may be disposable.

Accordingly, in one embodiment of D1, a bioreactor system is presented and includes a disposable container for housing biomaterials for processing, the disposable container including at least one input port, at least one exhaust port, at least one harvest port, a structure for supporting the disposable container, one or more sensors for sensing one or more parameters of the biomaterials in the container, a heater for heating the contents of the container, the heater having a thermostat and mixing system arranged with the system such that biomaterials contained in the disposable container are mixed. The disposable container may include **an impeller** plate affixed to a lower portion of the **flexible plastic bag**, where the impeller plate may include a post. The disposable container may also include an impeller hub mounted on the post, the impeller hub having at least one impeller blade arranged on the post and having at least one magnet. In yet another embodiment of D1 includes a bioreactor system which may include a support structure and a flexible plastic bag positioned within the support structure.

FIG. 8B is a schematic diagram illustrating an embodiment of the present invention which includes a bubble/air-lift mixing system (FIG. 7) and interior baffles in the support structure (FIG. 8A).

A bioprocess container forms the product contact surface for the bioreactor. The

container is preferable a flexible bag which may be placed in a rigid structure such as a tank shell for support.
In some embodiments of the invention of D1, the disposable bioreactor may comprise a plastic, flexible bag, but may also comprise a rigid material (e.g., plastic, metal, glass). The tank may be designed to include a height and diameter similar to standard stainless steel bioreactors. The design may also be scaleable down to small bench bioreactor volumes and up in excess of **1000 L** working volumes.
Sensors/probes and controls for monitor and controlling important process parameters include any one or more, and combinations of: temperature, pressure, pH, dissolved oxygen (DO), dissolved carbon dioxide (pCO2), mixing rate, and gas flow rate .
As shown, the bioreactor includes one or more ports 202 which may be used to add or withdraw gases and/or fluids from the bioreactor. A harvest or drainage port 204 is generally provided at the bottom of the bag so that gravity may be used to direct the contents out of the bioreactor.
In yet another embodiment of the invention of D1 (see FIGS. 7 and 8B) a bubble column or airlift system (utilizing bubbles of air/gas 701) is used with the disposable bioreactor bag-which provides for a mixing force by the addition of gas (e.g., air) near the bottom of the reactor. Such embodiments may include a bubble column 700, an air-lift fermenter 702 with internal draft tube 703 and an air-lift fermenter 704 with external draft tube. (see parag. of D1: 3,7,8,10-12,24,25,28,30,31-33,36,52)
The disclosure of D1 is therefore novelty destroying for the subject-matter of claims 1-62 in total.

2 DEPENDENT CLAIMS 2-35, 37-53, 55-62

The subject-matter which has been already destroyed by novelty cannot considered as involving an inventive step, because there is no contribution over the prior art.

Dependent claims 2-35, 37-53, 55-62 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.

3

Re Item VIII

Certain observations on the international application

Present claims 3-23,38-48 relate to a product defined (inter alia) by reference to the parameter as well as quotients and by the applicant defined ratios built up from specific parameters:
the ratio of :
- hight to volume
- a density of gas inlets per cross sectional area

the parameters of:
- an aeration rate at inlet
- a gas bubble volume
- an inlet gas pressure

The use of this parameter in the present context is considered to lead to a lack of clarity, because the claim does not clearly identify the products encompassed by it as the parameter cannot be clearly and reliably determined by indications in the description or by objective procedures which are usual in the art. This makes it impossible to compare the claims with the prior art. As a result, the application does not comply with the requirement of clarity under Article 6 PCT.

The claimed gas bubble volume of 20 to 1800 mm^3 and the inlet gas pressure of about 1-5 bar are a common gas bubble inlet and pressure value for a bioreactor equipped with gas supply.

The applicant is asked to provide a special technical effect based on the elaborated parameters and ratios.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003